- 1 Glasier AF, Cameron ST, Fine PM, et al. Ulipristal acetate versus levonorgestrel for emergency contraception: a randomised non-inferiority trial and meta-analysis. Lancet 2010; 375: 555–62.
- 2 Task Force on Post-ovulatory Methods of Fertility Regulation. Randomised controlled trial of levonorgestrel versus the Yuzpe regimen of combined oral contraceptives for emergency contraception. Lancet 1998; 352: 428–33.
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Anna Glasier and colleagues¹ report on a randomised non-inferiority trial to compare the efficacy and safety of ulipristal acetate with levonorgestrel for emergency contraception. They conclude that ulipristal acetate provides women and health-care providers with an effective alternative for emergency contraception that can be used up to 5 days after unprotected sexual intercourse.

As Giuseppe Benagiano and Helena von Hertzen suggest in their associated Comment,² this conclusion is at least premature and in fact misleading. The design of Glasier and colleagues' trial (drafted and funded by the manufacturer of ulipristal) lacks the attributes to prove the efficacy of ulipristal in preventing pregnancy up to 5 days after unprotected intercourse.

First, the sample size is too small to permit comparisons between ulipristal and levonorgestrel administered 73–120 h after unprotected intercourse from reaching significance.

Second, a superiority trial is needed to provide evidence that ulipristal should be implemented in current care, since this product is less accessible (need for prescription), more costly (three times the price of levonorgestrel in Belgium), and does not yet have the same safety data as levonorgestrel. This industry-driven publication fails

to support a change in current practice, where levonorgestrel is the first choice for emergency contraception if administered within 72 h of sexual intercourse and (if feasible) emergency insertion of a copper intrauterine device can be considered after 72 h. Further evidence is needed before a change in practice should be entertained.

We declare that we have no conflicts of interest.

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- Glasier AF, Cameron ST, Fine PM, et al. Ulipristal acetate versus levonorgestrel for emergency contraception: a randomised non-inferiority trial and meta-analysis. Lancet 2010; 375: 555-62.
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Authors' reply

Gilda Piaggio, Helena von Hertzen, Geert Herman Page, and Veerle Verhaeghe are unhappy with the methods or statistical analyses used in our published trial to compare levonorgestrel and ulipristal acetate for emergency contraception. The study was designed to provide a rigorous evaluation of efficacy in line with regulatory requirements for the approval of a new drug. As a registration trial, the protocol and statistical methods were reviewed by the US Food and Drug Administration before the start of the study, and the procedures, data collection, and analysis were subject to routine audit by independent quality assurance teams. Systematic pregnancy testing was done at enrolment and at follow-up, thereby ensuring accuracy and completeness of efficacy results.

Page and Verhaeghe criticise the trial for lacking the attributes to prove the efficacy of ulipristal acetate. Fundamental proof of efficacy of any method of emergency contraception would involve a randomised placebocontrolled trial. There has never been such a study, nor will there ever be one since no woman wanting to use emergency contraception to prevent unwanted pregnancy would be willing to use a placebo and no ethical committee

would ever give approval to such a study. Like everyone else, we have relied on indirect measures of effectiveness of the drugs and we will never know how many pregnancies any emergency contraceptive *really* prevents.

As we discussed in the paper, there is good evidence that ulipristal acetate is much more effective than levonorgestrel at preventing ovulation at the time in the cycle when conception is most likely to occur. Since we cannot get evidence of the true effectiveness of emergency contraception, biological plausibility of its effect is important. Yes, ulipristal acetate, as a new drug, is more expensive than levonorgestrel and purchasers will have to decide which emergency contraceptive product they provide on the basis of costeffectiveness calculations. However, for individual women who want to prevent pregnancy after unprotected sexual intercourse, surely a method that is more likely to prevent ovulation would be the method of choice.

AG has received grants from HRA Pharma and Bayer Schering, and is a scientific advisory board member of HRA Pharma. EG is Chief Executive Officer of HRA Pharma

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